UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/807,500	02/27/97	ZEICHER M	236007

EXAMINER

18N2/0121

CUSHMAN DARBY & CUSHMAN
PILLSBURY MADISON AND SUTRO
1100 NEW YORK AVE. NW
9TH FLOOR EAST TOWER
WASHINGTON DC 20005-3918

ART UNIT	PAPER NUMBER
1809	4

DATE MAILED: 01/21/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-27 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-27 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☑ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☑ received in Application No. (Series Code/Serial Number) 08/448,590.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40511

DETAILED ACTION

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an autonomous parvoviral vector containing the CAT (chloramphenicol acetyl transferase) gene or murine B7 gene under the control of the P38 promoter in place of the parvoviral genes encoding the parvoviral capsid proteins, does not reasonably provide enablement for nucleotide sequences or parvoviral vectors capable of effecting the destruction or normalization of any type of cancer cell or cells infected by any virus or bacteria *in vitro* or *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention is drawn to; (1) a nucleotide sequence comprising the nucleotide sequence of an autonomous parvovirus and at least one "effector sequence" which encodes an "effector polypeptide" or an antisense RNA or a ribozyme that is capable of effecting the destruction or normalization of any type of cancer cell or cells infected by any virus or bacteria. (2) a pharmaceutical composition comprising the nucleic acid as described above(3) and a method of treating cancer or infection by virus or bacteria. The claims as written read on both *in vitro* and *in vivo* applications.

The specification is totally prophetic in its disclosure of the claimed invention. The examples provided in the instant specification are limited to the expression of the CAT gene (example 9) and the murine B7 gene (example 7). Both the CAT gene and B7 gene are expressed by parvovirus vectors in transformed cells in culture and under the control of the P38 promoter. The specification as filed provides no examples that would show by correlation the broad scope of *in vivo/* therapeutic applications as instantly contemplated.

The invention as claimed is drawn to nucleotide sequences that contain an "effector sequence." The specification defines (page 9, third and fourth full paragraphs) an "effector sequence" as a nucleotide sequence which, when expressed, encodes an "effector polypeptide" capable of destroying or normalizing treated cells and a nucleotide sequence where, when transcribed is an antisense or ribozyme capable of destroying or normalizing treated cells. The scope of this definition includes innumerable polypeptides and antisense RNAs and ribozymes where the instant specification fails to provide guidance for such a broad scope. Claim 10 limits the "effector nucleic acid sequence" to nucleic acids that encode cytotoxic polypeptides, molecules that confer on a transfected cell sensitivity to a toxic agent, and a polypeptide capable of inhibiting tumor neoangiogenesis. These limitations do not limit the scope of the claimed invention as to be enabled. The specification prophetically suggests polypeptides that posses the above properties and gives no guidance or direction for other polypeptides that have these characteristics. There are no working examples either *in vivo* or *in vitro* for such polypeptides in a

parvoviral vector that will destroy or normalize a cancerous cell or virally or bacterially infected cells.

The claimed invention is drawn to ribozyme, antisense and gene therapy. A recent review by Stull et al discloses the many problems faced by artisans in the application of these systems *in vivo* and in cell culture. Stull discloses (page 476, left column second full paragraph) "[n]ucleic acid drugs must overcome several formidable obstacles before they can be widely applied as therapeutics. These obstacles require improving the stability of polynucleotide drugs in biological systems, optimizing the affinity and efficacy of the drug without reducing its selectivity, and targeting delivering nucleic acids across cell membranes." Stull et al further disclose(page 476 last paragraph bridging to page 477) " . . . none of the modalities proposed to date can eliminate the disease/target. Thus suppression of disease will require the continued presence of the agent until the disease is cured or the condition is eliminated . . . This makes treatment of chronic disorders such as HIV infection a difficult undertaking. An obvious solution to the persistence issue for agents that are composed of RNA is to have the patient produce their own medicine via the gene therapy route. This approach reduces the requirement for frequent administration but does not circumvent the other two issues, access and entry into the target cell." Stull further discloses in the subsequent paragraph "[i]f the target is outside the vascular system, the agent will have to extravasate. Non-gene nucleic acids drugs have molecular weights in the 3,000-10,000 Dalton range so extravasation is not a particular problem for the agent itself. However, as these drugs do not permeate into the cytoplasm of cells but are found primarily in the endosome compartment,

they will most likely require some covalent modification or delivery system to mediate their efficient entry into the cytoplasm of the target cell. Numerous delivery agents have been developed to facilitate uptake of oligonucleotides in cell culture. These include attempts to modify the ionic backbone, modifications to increase hydrophobicity(e.g., attachment of cholesterol) as well as attempts to attach a targeting ligand such as biotin or a neoglycoprotein directly to the nucleic acid drug. To date these efforts have led to improved uptake but not to improved cytoplasmic delivery."

The problems disclosed by Stull et al are apparent in the *in vitro* data in Example 7(Table 1) and in Example 9 of the instant specification. Table 1 shows the Fluorescence of cells transfected with a parvovirus containing the murine B7 gene. It is apparent that less than 1% of the 10,000 cells transfected expressed the B7 gene at any significant level. In Example 9 it appears that applicant admits that CAT expression is expressed at varying levels in different cell types which is indicative of the unpredictable nature of the art.

Dupont et al Disclose the use of an autonomous parvoviral vector for the expression of the CAT gene in transformed cells. Dupont et al disclose (page 1397 last full paragraph) "[t]his therapeutic approach implies designing a recombinant parvovirus based vector which(I) can be efficiently packaged into infectious viral particles, (ii) retain the parvoviral tropism for tumor cells, and (iii) selectively express a potent therapeutic gene such as one coding for a toxin, a prodrug, or a cytokine in order to increase the intrinsic parvoviral antineoplastic activity." The specification as filed does not provide guidance or direction or working examples for the selective expression of

such "therapeutic genes" and does not provide guidance or direction for providing high titer stocks that are required for therapeutic approaches. Dupont et al further disclose (page 1404 last paragraph) that the levels of viral DNA replication and the P38-driven expression of CAT are not necessarily correlated. This disclosure is indicative of the unpredictable nature of the art. Dupont et al disclose in the last paragraph of page 1405 that because some neoplastic cells such as B lymphocytes can escape transduction, which is presumed to be due to the lack of surface receptors for the viral vector, some of the natural tumors will constitute preferential targets for transduction by MVM-based vectors, while others could prove resistant. Dupont et al then state "[v]erifying this hypothesis implies evaluating potential oncoselective transduction mediated by MVM vectors both in vitro, with natural cancer tumor cell lines, and in vivo, with animals bearing model xenogenic or syngeneic tumor grafts." There is no guidance or direction and no examples in the specification as filed that would correlate to the oncoselective transduction of cancer cells or infected (viral or bacterial) cells with the vector of the claimed invention such that there is any destruction or normalization of any type of cancer cell or cells infected by any virus or bacteria *in vitro* or *in vivo*.

The invention as broadly claimed allows for the use of any promoter(claims 6 and 11) that is transactivated by factors specific for any medical condition. Claim 16 limits the invention to several such promoters. Claim 5 limits the invention to lack the P38 promoter. There are no working examples and no guidance in the specification as filed for the practice of the instant invention with any promoter other than the parvovirus P38 promoter such that the "effector

nucleic acid" is expressed and effects the destruction or normalization of any type of cancer cell or cells infected by any virus or bacteria *in vitro* or *in vivo*.

Because of the lack of guidance and lack of working examples in the specification as filed the invention as claimed is not enabled. One of skill in the art would have been led to perform undue experimentation to practice the invention as claimed. The undue experimentation would include: trial and error experimentation to determine what polypeptides, antisense RNAs, and ribozymes would effect the normalization or destruction of cancer cells or infected cells; overcoming the obstacles of gene therapy, antisense, and ribozyme systems as disclosed by Stull et al; determining a method for the production of high titre stocks of a parvoviral vector; to determine the level at which a specific gene will be expressed in a given cell type with any given promoter; and determining what promoter would function in a parvoviral vector to initiate appropriate levels of expression of a desired nucleic acid sequence product so as to destroy or normalize cancer cells or infected cells. Furthermore the invention is not enabled due to the unpredictability in the art, as is evidenced by the varying levels of expression of gene products in various transformed cell types and the lack of correlation in expression levels and vector replication in various transformed cell types disclosed by Dupont et al.

2. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The prior art of record and search does not teach a parvoviral vector wherein is contained a nucleic acid sequence that encodes a polypeptide or and antisense RNA or ribozyme

that is capable of effecting the normalization or destruction of cancerous cells or cells infected by virus or bacteria. Russell et al [J. Of Virology, Vol. 66(5):2821-2828, May 1992] disclose a parvoviral vector containing the genes for IL-2 and IL-4 to infect transformed cells in culture and express said genes.

3. Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims (and dependent claims) the terms ". . .capable of. . ." are vague and indefinite in that the capacity of a compound or composition to perform some function is a recitation of a latent characteristic of said compound or composition and such language carries no patentable weight. Redrafting the claims to read ". . .which. . .", for example would be remedial.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean McGarry whose telephone number is (703) 305-7028.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003.

Certain papers related to this application may be submitted to Art Unit 1809 by facsimile transmission. Papers should be faxed to Art Unit 1809 via the PTO Matrix Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see C.F.R. 1.6(d)). The Art Unit 1809 FAX number is (703) 308-4242 or (703) 305-3014. NOTE: If Applicant **does** submit a paper by Fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sean McGarry

January 12, 1998

GEORGE C. ELLIOTT
SUPERVISORY PATENT EXAMINER
GROUP 1800